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| EXAMINER | |
|---|---|
| ALLEN, MARIANNE P | |

| ART UNIT | PAPER NUMBER |
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| 1647 | |

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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/582,973 | NAKAMURA ET AL. | |
| | Examiner | Art Unit | |
| | Marianne P. Allen | 1647 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *06 January 2009*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-18* is/are pending in the application.

4a) Of the above claim(s) *18* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-18* are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

**DETAILED ACTION**

Applicant's arguments filed 1/6/2009 have been fully considered but they are not persuasive.

Claims 2-3 have been cancelled.

Claims 1 and 3-18 are pending and under consideration by the examiner.

The provisional rejection of claims 8-9 and 18 on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 7-8 of copending Application No. 11/041,363 is withdrawn as the 11/041,363 application is now abandoned.

***Election/Restrictions***

Claim 18 as amended is directed to an invention that is independent or distinct from the invention originally claimed for the following reasons: Claim 18 as amended is now directed to a gene therapy agent comprising DNA and a gene carrier. These products are classified in at least Class 514, subclass 44, and require a non-coextensive, non-patent literature search. The instant application was filed as the national stage filing of PCT/JP04/18719. As art can be applied against the invention of the original and amended claims 1 and 3-17, there is no single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical feature. A special technical feature must distinguish over the prior art.

Since applicant has received an action on the merits for the originally presented invention, this invention has been constructively elected by original presentation for prosecution

on the merits. Accordingly, claim 18 is withdrawn from consideration as being directed to a non-elected invention. See 37 CFR 1.142(b) and MPEP § 821.03.

***Double Patenting***

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1, 4, 6-7, and 17 are provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-5 and 18-21 of copending Application No. 10/926,088.

This rejection is maintained for reasons of record. Applicant's response acknowledges the rejection and requests that it be held in abeyance.

***Claim Rejections - 35 USC § 112***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim17 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 17 has been amended to be directed to non-glycosylated HGF as an active ingredient in combination with a conventional carrier or a binder. Basis is stated to be on page 28. This is not agreed with. Non-glycosylated HGF in combination with a conventional carrier or binder is only disclosed in the context of formulations to provide an injection, inhalant, suppository or oral agent. The claims are not so limited. For example, they embrace topical formulations.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13-16 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 14 requires enzymatic cleavage of sugar chains. However, recombinant production of the protein of claim 1 will not have any sugar chains to cleave. Clarification is requested.

Claims 13 and 15-16 recite DNA encoding HGF "having sugar chains" and/or "having no sugar chains." This is confusing. The DNA does not encode sugar chains. Glycosylation is a post-translational modification. Sugar chains are added if the appropriate amino acids are present in the translated amino acid and a suitable environment are provided such that glycosylation can occur. Particularly with respect to claim 16, there can be no gene comprising a base sequence encoding HGF having sugar chains. The DNA sequence implied by claim 1 is not a naturally occurring sequence. It is a mutated sequence and it is not a gene.

As written, recombinant production of HGF in **any** cell (see claims 10-13 and 15) or cell free protein synthesis system (see claim 16) will not result in any glycosylation because the translated protein has had all glycosylation sites mutated such that they cannot be glycosylated.

### *Claim Rejections - 35 USC § 103*

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any

evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4, 6-15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godowski et al. (U.S. Patent No. 5,316,921) in view of Shimizu (BBRC, 172:321-27, 1992).

Godowski et al. (U.S. Patent No. 5,316,921) discloses recombinantly producing glycosylation mutants of HGF by modifying the glycosylation sites, including N- and O-glycosylation sites. Production in yeast, insect cells, E. coli, and mammalian cells is disclosed. Post production enzymatic treatment is also disclosed. (See at least columns 14-15.) The five amino acid deletion form of instant SEQ ID NO: 2 is disclosed. (See column 2, lines 5-10.) Pharmaceutical compositions with conventional carriers are disclosed. Godowski et al. does not specifically disclose mutating the O-linked glycosylation site at amino acid 476.

Shimizu et al. discloses an O-linked glycosylation site at Thr-445 (corresponding to the instant amino acid position 476 of SEQ ID NO: 1 and instant amino acid position 471 of SEQ ID NO: 2) in human HGF. Removal of the oligosaccharide at this site by O-glycanase treatment did not change the activity of the HGF. See at least abstract and page 1334.

It would have been obvious to produce HGF that was completely carbohydrate free by mutating each glycosylation site so that it was not capable of glycosylation as suggested by Godowski et al. It would have been well known that unglycosylated HGF remained biologically active. Various forms of HGF that were enzymatically treated to remove carbohydrate structures

or that were produced in cells that could not glycosylate (such as E. coli) had been produced and remained biologically active.

Claims 1, 4-15, and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godowski et al. (U.S. Patent No. 5,316,921) in view of Shimizu (BBRC, 172:321-27, 1992) and further in view of Miyake et al. (U.S. Patent No. 7,125,688) and Miyake et al. (U.S. Patent NO. 7,129,064).

Godowski et al. and Shimizu et al. are applied as above but do not disclose feline or canine HGF.

Miyake et al. (U.S. Patent No. 7,125,688) discloses DNA sequences, vectors, and methods of producing feline HGF in E. coli. Recombinant production in E. coli would result in glycosylation deficient HGF. Pharmaceutical compositions are disclosed. See at least abstract, claims, and column 7.

Miyake et al. (U.S. Patent No. 7,129,064) discloses DNA sequences, vectors, and methods of producing canine HGF in E. coli. Recombinant production in E. coli would result in glycosylation deficient HGF. Pharmaceutical compositions are disclosed. See at least abstract, claims, and column 7.

It would have been obvious to mutate all of the glycosylation sites in feline and canine HGF as taught by Godowski et al. so that unglycosylated forms of feline and canine HGF could be produced in yeast or mammalian cells (cells capable of glycosylation). The glycosylation sites would have been known as taught by Godowski et al. and Shimizu et al. Both Miyake et al. references demonstrate that unglycosylated feline and canine HGF would have been useful.

Claims 1, 4, and 6-17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Godowski et al. (U.S. Patent No. 5,316,921) in view of Shimizu (BBRC, 172:321-27, 1992) and further in view of Patten et al. (U.S. Patent No. 6,365,377)

Godowski et al. and Shimizu et al. are applied as above but do not disclose a cell free synthesis system.

Patten et al. (U.S. Patent No. 6,365,377) discloses recombinantly producing a hepatocyte growth factor in a cell free system such as an E. coli lysate. The hepatocyte growth factor produced would be glycosylation deficient. See at least abstract, columns 21-23, and claims, particularly claim 24.

It would have been obvious to mutate all of the glycosylation sites in HGF as taught by Godowski et al. so that unglycosylated forms of HGF could be produced in all cell free systems as taught by Patten et al. The glycosylation sites would have been known as taught by Godowski et al. and Shimizu et al. Patten et al. demonstrates that unglycosylated HGF would have been useful.

Applicant's remarks concerning Oh-eda et al., Nissan et al., Naim et al., Cumming et al. and Gonzalez-Gronow et al. are not persuasive. These references do not concern glycosylation of HGF. The prior art of record amply documents that unglycosylated HGF would have been active. Mutating all glycosylation sites to prevent glycosylation would have been obvious to one of ordinary skill in the art. It would have made unglycosylated HGF more convenient to produce

and permitted production in additional host cells that would have been capable of glycosylation in the absence of such mutation (e.g. mammalian cells or yeast cells).

***Conclusion***

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Marianne P. Allen whose telephone number is 571-272-0712. The examiner can normally be reached on Monday-Friday, 5:30 am - 2:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Manjunath N. Rao can be reached on 571-272-0939. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Marianne P. Allen/
Primary Examiner, Art Unit 1647

mpa